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Augmentation of sebum secretion by *Propionibacterium acnes* through an increase in ABCB1-mediated transporter activity in differentiated hamster sebocytes

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Acne vulgaris is a chronic inflammatory disease in sebaceous glands and pilosebaceous units where excess sebum production and secretion are observed. *Propionibacterium acnes* (*P. acnes*), a Gram-positive anaerobic microbial species, is considered to play a role in the aggravation of acne. Although *P. acnes*, as well as peptidoglycan (PGN) from Gram-positive bacteria, has been reported to potentially augment the production of sebum in hamster sebaceous glands *in vivo* and *in vitro*, it is not fully understood whether *P. acnes* participates in the regulation of sebum secretion. In the present study, formaldehyde-fixed *P. acnes* (F-Acne) was found to increase not only the extracellular level of triacylglycerol (TG), which is a major component of sebum, but also the transporter activity using Rhodamine 123 in differentiated hamster sebocytes (DHS). In addition, the F-Acne-augmented extracellular TG level was decreased in the presence of an ABCB1 inhibitor, PSC833. Furthermore, the gene expression of ABCB1 was increased in the F-Acne-treated DHS. Similar augmentation of ABCB1-mediated TG secretion, transporter activity, and ABCB1 gene expression were detectable in PGN-treated DHS. Therefore, these results put forward novel evidence that *P. acnes* facilitates ABCB1-mediated TG secretion via PGN-induced signal pathways, under which ABCB1 gene expression is concomitantly enhanced in DHS. Moreover, these findings should accelerate the understanding of sebum secretion in sebaceous glands of acne patients, and may contribute to the development of acne therapy.

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Comparative activity of oral ivermectin and moxidectin in an experimental pig model of scabies

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Control of human scabies is hampered by limited number of suboptimal efficient therapies. The aim of our study was to use pigs as an animal model for testing new drugs like veterinary molecules (e.g.moxidectin MOX, macrocyclic lactones) with more attractive pharmacokinetic profiles that common treatment (i.e oral ivermectin IVM). We conducted a blind, controlled trial comparing oral IVM (200 µg/kg on days 0 and 10) with oral MOX (300 µg/kg at day 0) in pigs experimentally infested with *Sarocoptes scabiei* var *suis* at the veterinary college of Alfort, France using a previously described procedure. The study was approved by the Animal Ethics Committee. Pigs received 0.2mg/kg/d of dexamethasone to increase intensity and duration of scabies and were treated 9 weeks following infestation. 12 pigs (in 3 groups) were randomly assigned to IVM, MOX or no treatment-group. Every week, therapeutic monitoring was to score skin lesions and pruritus, to count mites and eggs in skin scrapings, to collect skin biopsies, blood samples for pharmacokinetics analysis of drugs and anti-Sarcoptes antibodies. The primary outcome was the complete absence of mites on day 14 post treatment. No adverse events were reported. The percentage reduction of mites count for the MOX-pigs was 50% at D2, 97.7% at D7 and 100% at D9 and 14. The percentage reduction of mites for the IVM-pigs was 20.7% at D2, 53.9% at D7, 95.9% at D9 and 83.4% at D14. For both groups, the decrease of eggs was 100%. After treatment, eggs from all three cohorts were able to hatch in an incubator (37°C, humidity 70%) indicating a suboptimal ovicidal activity of both drugs. As conclusion, a single dose of MOX seems to be effective and a promising alternative to the treatment of scabies.

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Involvement of HHV-6 infection in renal damage associated with DIHS/DRESS

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Drug-induced hypersensitivity syndrome/drug reaction with eosiophila and systemic symptoms (DIHS/DRESS) is one of the severe drug eruption with fever, lymphadenopathy, human herpesvirus 6 (HHV-6) reactivation, and multiple organ failure. Renal failure is occasionally observed in DIHS/DRESS patients, and affects the prognosis of the patients. However, the pathogenesis is still unknown. In this study, we studied the patient who developed renal failure during the course of DIHS/DRESS, and found that HHV-6 infection was involved in the development or triggering of renal failure. A 62-year-old Japanese man developed high fever, systematic erythema and bilateral cervical lymphadenopathies on day 28 after receiving trimethoprim/sulfamethoxazole (TMP/SMX). HHV-6 DNA was detected in peripheral blood mononuclear cells (PBMC) on day 21 after onset (2×10 copies/ml). He was diagnosed as DIHS/DRESS due to TMP/SMX. His symptoms immediately disappeared after the withdrawal of TMP/SMX and induction of systemic steroid therapy. However, he developed acute renal failure that necessitated hemodialysis on day 79 after onset. HHV-6 DNA was also detected in urine (2×10 copies/ml). He subsequently died from opportunistic infection and multiple organ failure despite intensive therapy. The autopsy examination revealed interstitial nephritis with an intense lymphocytic infiltrate and tubular necrosis. Viral load of HHV-6 were significantly increased in autopsy renal specimens from this patient (8×10^4 copies/100mg), compared to specimens of other organs. Furthermore, HHV-6 antigens were detected in the tubular epithelial cells by immunostaining with anti-HHV-6 monoclonal antibody. This is the first biologically and histologically proven report on the relationship between renal failure and HHV-6 infection during the course of DIHS/DRESS. We considered that HHV-6 may be associated with development or triggering of renal failure related to DIHS/DRESS.

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Telaprevir-induced drug eruption

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Telaprevir is a protease inhibitor used in the treatment of chronic hepatitis C genotype 1 infection. We present four cases of telaprevir-induced skin eruption including a novel case of telaprevir-induced vasculitis with a literature review. The first patient was a 61-year-old male with a two-week history of a generalized eczematous eruption that started on his buttocks and subsequently spread to involve his trunk and limbs. The rash developed seven weeks after commencing telaprevir. A skin biopsy showed subacute spongiotic dermatitis. The second case was a 57-year-old male who presented with a four-week history of a palpable purpuric rash on his legs which began eight weeks after starting telaprevir. Skin histology confirmed the diagnosis of cutaneous vasculitis. The third patient was a 50-year-old male who presented with a generalized eczematous eruption within one week of commencing telaprevir. The fourth and final case was a 60-year-old female who presented with an extensive eczematous eruption, which developed twelve weeks after commencing telaprevir. The patient was admitted to hospital with pancytopenia. Telaprevir was discontinued and the rash subsided following treatment with topical corticosteroids. All four patients were systemically well, with no mucous membrane involvement. All patients were treated conservatively and did not require systemic steroids. All eruptions gradually resolved over up to six weeks after completion of telaprevir treatment. Telaprevir-induced rash is the most common adverse effect associated with the drug, and occurs in 51% of patients. In its most severe form, patients are required to stop treatment. Case 2 described above highlights the awareness of a vasculitic-type rash which has not previously been reported in telaprevir-treated patients. A collaborative effort between dermatologists and hepatologists may improve the tolerability of telaprevir in patients with moderate to severe telaprevir-induced eruptions as demonstrated in our case series.

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TGFBeta Induced HIV-1 Restriction in Langerhans cells

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Our study aims to decipher restrictions of HIV-1 infection in Langerhan cells (LC). For this purpose we employed two LC cell models, monocytes derived LC and MUTZ-3 derived LC, as well as primary Langerhan cells freshly isolated from skin explants. We show that SAMHD1 is expressed in LCs but in contrast to myeloid DCs, the degradation mediated by Vpx did not result in rescue of HIV-1 infection in LCs models. Importantly, Vpx-mediated degradation of SAMHD1 in dermal DCs freshly isolated from human skin led to a strong increase of HIV-1 replication. On the contrary, down-regulation of SAMHD1 expression in skin-derived LCs did not result in a statistically significant enhancement of HIV-1 infection. The restriction activity in LCs was induced by TGF-β and was present in immature LCs at a steady-state. Additionally, maturation of LC with bacteria components diminished LC restrictive phenotype, which explains why HIV acquisition is increased during co-infection. In conclusion, we report a novel TGF-β-dependent HIV-1 post-entry restriction activity, which is specifically present in immature LCs and potently protects these cells from HIV-1 infection. Modulating or enhancing this natural resistance of LCs to HIV-1 infection may offer novel avenues to block HIV-1 in its early stages of transmission.